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EXAMINER

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FOLEY & LARDNER
RING STREET STATION
1800 DIAGONAL ROAD SUITE 500
P O BOX 299
ALEXANDRIA VA 22313-0299

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 21-29 are pending in the applica
   Of the above, claims _____ are withdrawn from considerati
2. ☒ Claims 1-20 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 21-29 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been recei ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Part III DETAILED ACTION

Priority

1. Although this application filed under 37 C.F.R. § 1.60 has included the necessary reference to the prior applications, the present status of all parent applications should be included. The phrase "now abandoned" should follow the filing dates of all the parent applications (if this is indeed their current status).

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Currently, the claimed invention is directed to methods of stimulating or inhibiting epithelial cells using KGF or antibodies to KGF, respectively. Appropriate correction is required.

3. The Figures and Tables of the instant application are labeled with Roman numerals followed by Arabic numerals as well as letters. 37 C.F.R. § 1.84 (U) (1) states that different views must be labeled in consecutive Arabic numerals, independent of the numbering of the sheets and partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. For example, this application contains figures I-1 through I-5 and II-1 through II-3; these figures should be renumbered as Figures 1 through 8 (also, renumbered Figures 2 and 6 should be 2A-2C and 6A-6C in order to correctly refer to subparts). The tables should also be numbered with Arabic numerals rather than I-1, I-2, and II-1; since the tables were submitted separately rather than being incorporated into the specification, they should also be referenced as Figures (see form PTO 948). If the Tables are to

remain as tables, they should be directly incorporated into the specification at the first point of reference. Also, if they are to remain as Tables, their reference in the Brief Description of Drawings should be removed because they, at that point, are not drawings. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (U) (1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly. Also, the Figures contain legends which are very long and include methods associated with the Figures. Applicants are directed to the MPEP and 37 C.F.R. §1.84 (o) regarding Figure Legends; "they should contain as few words as possible". Applicants are advised that descriptive material should not be included in the Figures and Figure Legends should contain only information necessary for fully understanding the figures (i.e. symbol definitions or clarification control and test conditions). Appropriate correction is required.

4. The Abstract of the Disclosure is objected to because it does not describe the claimed invention. Correction is required. See M.P.E.P. § 608.01(b).

5. Applicant is reminded of the proper content of an Abstract of the Disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art **to which the invention pertains.**

If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure.

If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement.

In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof.

If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

In the process of amending the specification to remove reference abbreviations and to incorporate the actual references, Applicants failed to correct the entire specification. For example, at page 58, line 10, the reference "II-3" has not been replaced; at page 63, lines 5-6 and 8, references "II-21" and "II-22" have not been replaced. Applicants should carefully read the specification for any other errors that need correction, as there may be others that were missed.

Objections and Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

With regard to claims 21-26, the specification describes the isolation and purification of a growth factor specific for epithelial cells; KGF. This growth factor stimulates DNA synthesis (page 38) as well as epithelial cell proliferation (page 39). The stimulatory effects of KGF and FGF (acidic and basic) on epithelial cells (BALB/MK cells) and fibroblasts are summarized in Table I-1, wherein KGF does not stimulate fibroblasts. This disclosure, which is limited to stimulation of epithelial cells, and more specifically, to BALB/MK cells, is not enabling for methods of treating (a patient) requiring specific stimulation of epithelial cells or a method of accelerating or improving wound healing involving the epidermis, as required by the claims, because the actions of growth factors *in vitro* do not correlate with the actions of the same growth factors *in vivo*. (See Meyer-Ingold; especially page 389, column 2, paragraph 2). Many factors, which are not present and can not be predicted from an *in vitro* model, affect the ability of a growth factor to affect a particular cell. Two very important factors which influence *in vivo* activity of therapeutic proteins are pharmacokinetics (adsorption, distribution, metabolism, excretion) and immunogenicity (neutralizing antibodies, altered pharmacokinetics, sensitization). When looking at pharmacokinetics alone, it is not predictive that the growth factor will even be able to reach the site of action. In the case of wounds, the site of action

is under a great state of flux, and it is not predictive that the growth factor would even survive the wound environment (proteolytic enzymes, ischaemia, altered tissue dynamics, etc.) or remain at the wound site long enough for it to be able to act. *In vitro*, the addition of a growth factor to a cell culture guarantees that the growth factor is going to reach its site of action, however, this is not the case *in vivo*. *In vivo* use of growth factors also adds the complications of immunogenicity that are not present *in vitro*, and it is not predictive what effect these factors will have on the ability of a growth factor to act specifically as *in vitro*. The disclosure of the specification also fails to address the issues of efficacy, toxicity, or dose/response kinetics, all of which are immensely important if a growth factor is to be used in a method of treatment. In order for a protein to actually have an action *in vivo*, receptors for that protein must be present at the intended site of use. As of 1993, a receptor for KGF was identified in mice, but the role of KGF in wound healing was unknown (Bennett et al., Am. J. Surg. 165: 728-737, 1993). The specification fails to provide any examples of the use of KGF *in vivo* to stimulate epithelial cells or to treat wounds, and although *in vivo* experiments are not necessary for the enablement of an invention, the use of growth factors *in vivo* has been established as unpredictable and a nexus between *in vitro* experiments and *in vivo* use of growth factors has not been established. Also, the growth factor of the instant invention (KGF) is a novel growth factor, and the skilled artisan only has the teachings of the instant specification to guide him/her. Therefore, it would require undue experimentation of one of

ordinary skill in the art to practice the claimed invention, absent evidence to the contrary.

With regard to claim 27, the specification describes the neutralizing antibodies to KGF (page 31-32), monoclonal mouse antibodies (page 56), and polyclonal rabbit antibodies (page 56). The specification does not provide any examples or strategies for a method of treating conditions that require specific inhibition of epithelial cells comprising administration of an antibody. There is insufficient information or nexus with respect to the ability of KGF antibodies (monoclonal, polyclonal, or neutralizing) to inhibit epithelial cells for treating conditions. Pharmaceutical therapies (especially utilizing antibodies) are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein by be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown; may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

As discussed previously, the *in vitro* and animal model studies involving growth factors have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on *in vitro* binding and functional inhibition

studies accurately reflects the relative efficacy of the claimed therapeutic method. The specification describes several types of antibodies (neutralizing, monoclonal, polyclonal, murine, rabbit), but the specification is deficient in teaching which, if any, of these antibodies is effective in specifically inhibiting epithelial cells. The claimed method encompasses the use of an antibody (any antibody) against KGF to specifically inhibit epithelial cells, however, other factors (especially aFGF) also stimulate epithelial cells (see Table I-1). It has not been established that the inhibition of a single growth factor would be effective for inhibiting epithelial cells and a person of ordinary skill in the art would not reasonable expect that the mere inhibition of KGF would result in inhibition of epithelial cells. With regard specifically to the enablement of the use of an antibody therapeutically, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for *in vivo* human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). Humanized antibodies may still present serious problems with immunogenicity, since the idotype of such antibodies will contain unique amino acid sequences.

The specification does not provide sufficient information or nexus *a priori* that establishes the efficacy of the instant method for the treatment of a condition. In the absence of clear and convincing evidence commensurate in scope with the claims, it appears that undue experimentation would be required of one skilled in the art to

practice the instant invention using the teaching of the specification alone. The specification does not adequately teach how to effectively treat any disease or condition or reach any therapeutic endpoint in humans by administering antibodies to KGF. The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the development of effective in vivo therapeutic methods, commensurate in scope with the claimed method. Furthermore, the specification does not even provide examples of in vitro binding inhibition assays. Therefore, it is not clear that the skilled artisan could predict the efficacy of the claimed method for treating conditions requiring specific inhibition of epithelial cells, encompassed by the claims.

7. Claims 21-27 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

8. Claims 21-29 are further rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited as outlined below. In addition to the specification failing to provide an enabling disclosure for the claimed methods, the claims are also broader than the disclosure of the specification. Therefore, additional rejections are being made in order to specifically point out the deficiencies of the specification with regard to the scope of the claims (this does not constitute an admission that the claims are enabled, but rather serves to point out further problems

of enablement of the claims, with regard to the scope of the claims and the disclosure of the specification). See M.P.E.P. §§ 706.03(n) and 706.03(z).

The instant claims 21, 22, 26, and 28 (and dependent claims) are also currently broader than the enabling disclosure and the disclosure is enabling only for claims limited to human KGF having a molecular weight between 16 and 30 kDa as determined by migration in NaDodSo4/PAGE, and a specific activity of about 3.4 x 10^4 to 3.2 x 10^5 units per milligram of protein, where one unit of activity is defined as that amount which causes half of the maximal possible stimulation of DNA synthesis in BALB/MK keratinocyte cells under standard assay conditions or for human KGF having the amino acid sequence of Figure II-1B. The claims are drafted in such breadth that the claims cover all compositions containing a protein having a molecular weight of between 16 and 30 kDa and having human KGF specific activity in excess of 3.4 x 10^4 units per milligram of protein regardless of the process used to achieve the purification and regardless of the degree of purity achieved. There is no evidence of record regarding the upper limit of specific activity for KGF. It is conceivable that the upper limit of activity for KGF may be 10 to 20 fold higher than that achieved utilizing the disclosed process and therefore, the claims are broader in scope than warranted by the enabling disclosure. The specification has not provided guidance to the skilled artisan as to how to obtain KGF with a specific activity greater than what is disclosed, and therefore, the skilled artisan would not know how to use KGF with an unlimited activity in the claimed methods. Future modifications

to the protein (amino acid substitution, purification procedures, etc.) may provide for a specific activity which is significantly greater than that which is disclosed in the instant specification, modifications for which there is no guidance in the specification. It would not be predictive that one of ordinary skill in the art could obtain KGF with an unlimited specific activity, such activity being encompassed by the claims. Nor does the specification disclose methods of purifying or obtaining KGF with a higher specific activity than that already described. Undue experimentation would be required by a person of ordinary skill in the art to obtain KGF with a specific activity that is greater than the activity disclosed in the specification because there is no guidance in the specification to enable one of ordinary skill in the art as to how a greater activity could be obtained. As mentioned previously, modifications of the protein could increase the activity of the protein, but the specification has not provided guidance as how to modify the protein to increase its specific activity. Different purification methods may be able to increase the specific activity of the protein, but additional methods are not provided in the specification. In conclusion, it is determined undue experimentation would be required to obtain KGF with a specific activity greater than what is disclosed in the specification and that claims to "a specific activity of at least about" are broader than the enabling disclosure for the reasons stated above, absent evidence to the contrary.

Claim 27 encompasses a method utilizing antibodies "against a polypeptide selected from the group consisting of a polypeptide comprising a unique portion of

the amino acid sequence in Figure II-1B, a polypeptide comprising an amino acid sequence as presented in Figure II-1B wherein the N-terminus is cysteine 32 and the C-terminus is threonine 194, and a polypeptide comprising an allelic variant of human KGF". These claims are currently broader than the enabling disclosure in that they are drafted in such breadth that the claims cover antibodies to all possible amino acid sequences comprising "a unique portion of the amino acid sequence in Figure II-1B". In the narrowest terms, this could be a polypeptide having the amino acid sequence of Figure II-1B, however, the skilled artisan would not know what a unique portion would be because no function or structure is associated with this unique portion. The specification does not provide guidance to one of ordinary skill in the art as how to make an antibody to a polypeptide comprising a unique portion of the amino acid sequence in Figure II-1B. The claim does not define what would constitute a "unique portion" and the skilled artisan would not be able to determine, based on the disclosure of the specification, what would constitute a unique portion without further guidance from the specification. The specification describes this protein as being novel, therefore, any portion of the protein may constitute a unique portion. The claim encompasses a method of treating requiring specific inhibition of epithelial cells, said method comprising the administration of an antibody to KGF. In order for this antibody to inhibit epithelial cells, the antibody would need to bind to the ligand specifically. As the specification points out (see Figure II-2), KGF is a member of the FGF family and has a high degree of identity with the other FGF's. In

order for the antibody to be specific, it would need to recognize an epitope of KGF that is not found on the other FGF peptides. It would require undue experimentation to determine which portions of the protein of Figure II-1B are "unique" and that would provide an appropriate epitope for the generation of antibodies that would specifically inhibit epithelial cells. The claims also encompass antibodies to allelic variants of KGF. It is well known in the art that allelic variants of proteins exist and allelic variants are always obvious over the protein if there are no unexpected properties of the allelic variants. However, the specification has not provided guidance to the skilled artisan as to which allelic variants actually exist for the claimed KGF. If the allelic variants do not have a specific epitope to which antibodies could be raised, the skilled artisan would not know how to use these antibodies to the variants in the claimed method. Furthermore, because the specification does not describe any allelic variants, the skilled artisan would not know how to make allelic variants which could be used to create antibodies for the claimed method. Amino acid substitution, deletion, addition, truncation, etc. is not a predictive event, therefore, it would require undue experimentation for one of ordinary skill in the art to make and use antibodies in the claimed method wherein the antibodies are against allelic variants because the specification has provided no guidance as what would constitute an allelic variant or which allelic variants could be used in the same manner as the KGF of the instant application, absent evidence to the contrary.

Claims 24, and 27 encompass a method of stimulating/inhibiting epithelial cells using KGF or antibodies to KGF, wherein the KGF is human KGF polypeptide *comprising* an amino acid sequence. From the specification, it is clear that the amino acid sequence of Figure II-1B represents the human KGF polypeptide. The specification has not provided any guidance as to which amino acids could be added to this amino acid sequence and still obtain a protein with the activity and functions of human KGF. The language of the claim is open (i.e. comprising) and therefore, the amino acid sequence of Figure II-1B could contain other amino acids, non-naturally occurring amino acids, chemical modifications, fusion proteins, etc. The specification has not provided examples or guidance to the skilled artisan to enable a human KGF polypeptide comprising an amino acid sequence because it is not predictive which modifications or amino acid additions or fusions could be made to the KGF protein and still obtain a protein which could be used as disclosed in the specification. It would require undue experimentation of one of ordinary skill in the art to determine which of a multitude of modifications, additions, fusions could be made to the KGF protein, absent evidence to the contrary.

Claim 25 is broader than the enabling disclosure in that the specification has not adequately described functional domains which will allow the skilled artisan to create a protein as claimed. There is inadequate guidance in the specification as to which amino acids would provide functional domains or be responsible for preferential mitogenic activity or be responsible for heparin sensitivity. The

specification has not provided sufficient guidance for the skilled artisan to pick and choose amino acid sequences that can be combined in order to create a protein with the desired activities of KGF. There is inadequate structure-function information provided by the specification to teach what essential features of the amino acid sequence encoding human KGF are germane to achieving a protein with the activity of native KGF. Thus, it would require undue experimentation for one skilled in the art to make proteins or chimeric polypeptides that meet the broad limitations of the instant claims without further guidance from the specification, absent evidence to the contrary.

9. Claims 21- 28 (and dependent claim 29) are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 21, 22, 26, and 28, language of "a specific activity of at least about" does not provide an upper limit of activity. Because there is no upper limit of activity, one of ordinary skill in the art would not be able to determine the metes and bounds of the claimed invention and therefore, the claims are indefinite.

Also in these claims, a keratinocyte growth factor is characterized by a specific activity in units per milligram of protein, but the claims do not define what constitutes a unit of activity. Without knowing to what a unit of activity corresponds, the skilled artisan is not able to determine the metes and bounds of the

claimed invention. The specification supports an activity "where one unit of activity is defined as that amount which causes half of the maximal possible stimulation of DNA synthesis in BALB/MK keratinocyte cells under standard assay conditions" and addition of language such as this may obviate this ground of rejection.

Claims 23, 24, and 27 are indefinite and unclear because of the recitation "wherein the N-terminus of the polypeptide is cysteine 32 and the C-terminus is threonine 194". It is not clear if Applicants intend the numbers to indicate amino acid positions. If this is the case, language such as "cysteine at amino acid 32 and the C-terminus is threonine at amino acid 194" would obviate this ground of rejection.

Claim 25 encompasses chimeric polypeptides comprising "functional domains" and "a different member of the FGF family". This language is indefinite and unclear because one of ordinary skill in the art would not know what constitutes a "functional domain" or a "different member". A functional domain could be an antibody domain, a receptor binding domain, a protein binding domain, a hydrophobic domain, etc. and therefore, the metes and bounds of the claims cannot be ascertained. With regard to "a different member", what is a different member and what is different about it (with respect to what or compared to what)?

In claim 27, language of "a unique portion of the amino acid sequence in Figure II-1B" is indefinite and unclear because the skilled artisan does not know what constitutes a "unique portion". The specification does not provide a definition of "unique portion" nor are the metes and bounds of the claim ascertainable from this

language. This ground of rejection would be obviated if Applicants would distinctly claim the amino acid sequence which is deemed to be the unique portion of Figure II-1B.

Claims 21-29 are indefinite because the claims are directed to generic methods of stimulating or inhibiting epithelial cells. The claims do not specifically state what is being stimulated or inhibited. For example, a substance could stimulate/inhibit cell proliferation, cell growth, cellular secretion, cellular adhesion, cellular signalling, etc. The claims should specifically state what process is being stimulated or inhibited.

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 4PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor for Art Unit 1812 can be reached via the Group receptionist at (703) 308-0196. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
June 6, 1996
CA

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800